

CLAIMS

1. A polypeptide comprising a splice variant of an ErbB ligand encoded by differential exon usage comprising a truncated EGF domain devoid of the C-loop of the EGF domain.
2. The polypeptide according to claim 1 wherein the splice variant comprises a truncated ErbB receptor modulating EGF domain comprising only the first four of the six conserved cysteines found in an intact EGF domain.
3. The polypeptide of claim 2 wherein the fourth conserved cysteine of the truncated ErbB receptor modulating EGF domain is the penultimate amino acid at the C terminus of the polypeptide.
4. The polypeptide according to claim 3 having the sequence set forth in any one of SEQ ID NOS:73 to 84.
5. The polypeptide according to claim 3 having the sequence of any one of SEQ ID NOS: 93, 95-104, 109-121.
6. The polypeptide according to claim 2 wherein the splice variant comprises a receptor-modulating EGF domain having only the first four of the six conserved cysteines found in an intact EGF domain, further comprising an amino acid sequence encoded by an alternative exon other than the second exon encoding conserved cysteines five and six of the intact ErbB receptor-modulating EGF domain.
7. The polypeptide according to claim 6 having the sequence of any one of SEQ ID NOS:111-121.
8. The polypeptide according to claim 2 wherein the splice variant comprises a receptor modulating EGF domain having only the first four of the six conserved cysteines found in an intact EGF domain, wherein the splice variant has at least 90% homology to the aligned amino acid sequence of the same fragment in the EGF domain of a known ErbB ligand between cysteine 1 and cysteine 4.
9. The polypeptide of claim 8 wherein the splice variant has at least 95% homology to the aligned amino acid sequence of the same fragment in the EGF domain of a known ErbB ligand between cysteine 1 and cysteine 4.
10. The polypeptide of any one of claims 1 to 9 wherein the N terminal flanking sequences preceding the cysteine 1 are at least 90% homologous to the same

sequence in the EGF domain of a known ErbB ligand.

11. The polypeptide of any one of claims 1 to 9 wherein the splice variant retains binding activity to at least one member of the ErbB/EGF receptor family.

12. The polypeptide of claim 10 which retains binding activity to the receptor cells with significantly reduced biological activity compared to an equimolar concentration of at least one known agonist ligand.

13. The polypeptide of any one of claims 1 to 9 wherein the splice variant exerts inhibitory activity on at least one member of the ErbB/EGF receptor family.

14. The polypeptide of claim 10 which exerts inhibitory activity to the receptor when in a 100-fold molar excess or less, to at least one known agonist ligand.

15. An isolated polynucleotide encoding a splice variant of an ErbB ligand comprising a truncated ErbB-Receptor-modulating EGF domain devoid of the C-loop of the EGF domain.

16. The polynucleotide according to claim 15 wherein the splice variant comprises a truncated receptor-modulating EGF domain comprising only the first four of the six conserved cysteines found in an intact EGF domain.

17. The polynucleotide of claim 16 wherein the fourth conserved cysteine of the encoded truncated ErbB-Receptor modulating EGF domain is the penultimate amino acid at the C terminus of the polypeptide.

18. The polynucleotide according to claim 17 comprising the sequence of any one of SEQ ID NOS:128 to 139.

19. The polynucleotide according to claim 17 having the sequence of any one of SEQ ID NOS:148 to 165.

20. The polynucleotide according to claim 16 wherein the encoded splice variant comprises a receptor-modulating EGF domain having only the first four of the six conserved cysteines found in an intact EGF domain, further comprising an amino acid sequence encoded by an alternative exon other than the second exon encoding conserved cysteines five and six the of the intact ErbB receptor-modulating EGF domain.

21. The polynucleotide according to claim 20 having the sequence of any one of SEQ ID NOS:166-182.

22. The polynucleotide according to claim 16 wherein the splice variant comprises a receptor modulating EGF domain comprising only the first four of the six

conserved cysteines found in an intact EGF domain, wherein the splice variant has at least 90% homology to the aligned amino acid sequence of the same fragment in the EGF domain of a known ErbB ligand between cysteine 1 and cysteine 4.

5 23. The polynucleotide of claim 21 wherein there is at least 95% homology to the aligned amino acid sequence of the same fragment in the EGF domain of a known ErbB ligand between cysteine 1 and cysteine 4.

10 24. The polynucleotide of claim 21 or claim 22 wherein the encoded N terminal flanking sequences preceding the cysteine 1 are at least 90% homologous to the same sequence in the EGF domain of a known ErbB ligand.

25. The polynucleotide of any one of claims 15 to 21 wherein the splice variant exerts inhibitory activity to at least one member of the ErbB/EGF receptor family.

15 26. The polynucleotide of claim 25 which encodes a polypeptide that exerts inhibitory activity to the receptor on cells with significantly reduced biological activity compared to an equimolar amount at least one known agonist ligand.

27. An antisense oligonucleotide capable of specifically inhibiting the expression of a polypeptide according to any one of claims 1-14.

20 28. A polynucleotide construct comprising an isolated polynucleotide encoding the splice variants of any one of claims 1-14.

29. A vector comprising the isolated polynucleotide encoding the splice variants of any one of claims 1-14.

30. A host cell transformed with a polynucleotide encoding the splice variants of any one of claims 1-14.

25 31. A host cell transformed with a polynucleotide according to any one of claims 15-26.

32. A pharmaceutical composition comprising as an active ingredient a polypeptide according to anyone of claims 1-14.

30 33. A pharmaceutical composition comprising as an active ingredient a polynucleotide according to anyone of claims 15-26.

34. A pharmaceutical composition comprising as an active ingredient a antisense oligonucleotide according to claim 27.

35. A method of treating a disease or disorder related to an ErbB receptor in

an individual in need thereof comprising administering to the individual a therapeutically effective amount of a polypeptide according to any one of claims 1-14.

36. The method of claim 35 wherein the disease or disorder is selected from a neoplastic disease, a hyperproliferative disease, angiogenesis, restenosis, wound healing, psychiatric disorders, neurological disorders and neurological injuries.

37. A method of treating a disease related to pathological activity of at least one ErbB receptor comprising administering a therapeutically effective amount of a polynucleotide according to any one of claims 15-26.

38. The method of claim 37 wherein the disease or disorder is selected from a neoplastic disease, a hyperproliferative disease, angiogenesis, restenosis, wound healing, psychiatric disorders, neurological disorders or neural injury.

39. A method for selectively enhancing or promoting the proliferation or differentiation of stem cells expressing ErbB receptors, comprising exposing the stem cells to an ErbB ligand splice variant, according to any one of claims 1-14.

40. The method of claim 39 wherein the stem cells are of neural, cardiac or pancreatic lineages.